REMARKS

Claims 29, 32-33, 36-37 and 40 are currently pending. Claims 32 and 36 are amended as required by the Examiner to recite only the exact conditions used, not the range incorporated thereby.

a) Written Description

The Examiner has rejected claims 32 and 36 as failing to comply with the written description requirement, because allegedly only those conditions actually demonstrated in the examples are supported by the specification, and not the range therebetween. Applicants do not acquiesce in this parsimonious application of Section 112, but in order to advance the prosecution have made the amendment insisted on by Examiner.

b) Indefiniteness

The Examiner has rejected claims 29, 32-33, 36 and 40 as being indefinite. Applicant neglected to address this issue in the last Response to Office Action. The term at issue is "slowly maximally inhaling."

The term "slowly maximally inhaling" is not indefinite, but rather is a term of art with an art accepted meaning.[1] Many researchers in the field of inhalation therapy have used the exact

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[1] *See e.g.,* Roller et al., *Spacer inhalation technique and deposition of extrafine aerosol in asthmatic children*, Eur. Respir. J. 29:299-306 (2007) ("children used a **slow maximal inhalation**"); Barbnen *et al., Effect of detergent-coated versus non-coated spacers on bronchodilator response in children with asthma*, J. Paediat. Child Health 39(4): 270-273 (2003) ("perform a **slow maximal inhalation**, followed by a breath hold"); Devadason *et al., The Effect of Inhalation Technique, Spacer Volume and Training on Aerosol Delivery from Spacers in Children*, Presented at the American Thoracic Society Conference, May, 2005, San Diego, CA. (discussing inhalation study using "one **slow maximal inhalation**" and stating "The single **maximal inhalation** technique increased drug delivery to patients compared to tidal breathing."): US20050051161 (The alerting inhaler has a smaller air flow tube, with a front air inlet closed by a cover with a hole for **slow, deep inhalation**."). See also

phrase "slow maximal inhalation" or the similar phrase "slow deep inhalation." As such the phrase cannot be indefinite. *Abbott Labs. v. Andrx Pharms., Inc.*, 473 F.3d 1196, 1209 (Fed. Cir. 2007) ("'the ordinary and customary meaning of claim term is the meaning that the term would have to a person of ordinary skill in the art in question.'") (cite omitted).

Further, the meaning of the phrase is even readily apparent to any asthmatic or other patient using metered dose inhalers and requires little more to understand than the application of the widely accepted meanings of the common words applied in the context of inhalation. All inhalers function by directing the spray into the open mouth while "slowly maximally inhaling." That is, one should inhale slowly, not quickly, and one should inhale as deeply as possible to allow the inhalant to penetrate as far into the lungs as possible. In other word, one should take the drug by slowly maximally inhaling. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) ("In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words.").

Because the term has a customary meaning in the art and that meaning is in accordance with the meaning of the commonly understood words making up the phrase, it cannot be indefinite. Therefore, Applicants request the indefiniteness rejection be withdrawn.

c) *Prima facie* Obviousness Case

The *prima facie* obviousness burden lies on the Examiner to show at least the following: 1) that the art teaches every element of the claimed invention,[2] 2) that there is a motivation to combine or modify the art,[3] and 3) that there is a reasonable expectation of success in making

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http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a601042.html showing inhalation instructions ("Take a **slow, deep breath** through the mouthpiece"). (Emphasis added to each).

[2] *See e.g.*, MPEP 2143.03 ("All Claim Limitations Must Be Taught or Suggested").

[3] KSR did not negate the motivation to combine test, but only cautioned against its rigid application. *KSR Int'l Co. v. Teleflex Inc.*,127 S. Ct. 1727, 1741 (U.S. 2007) ("When it first

that combination or modification. While the expectation of success need not be absolute, there does need to be a **reasonable** expectation of success. *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 417 F. Supp. 2d 341, 371 (Fed. Cir.2006) ("While a reasonable expectation of success must be shown, in order to show *prima facie* obviousness it is not necessary to show that success was absolutely predictable."); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (discussing the obviousness case and stating that one element is "whether the prior art would also have revealed that . . . those of ordinary skill would have a reasonable expectation of success.").[4] If the *prima facie* case is made, it can be rebutted by showing long felt need, commercial success, unexpected results,[5] or teaching away. *See e.g.*, *KSR Int'l Co. v. Teleflex Inc.*,127 S. Ct. 1727, 1734, 1740 (2007).

d) Sequestration and Dosage Elements Missing

Examiner has failed to cite **any** art describing the missing element "allowing said monomeric FIX to deposit in the deep lung tissue such that said monomeric FIX is sequestered in said deep lung tissue" and "providing sufficient FIX to prevent bleeding for at least 100 hours after administration." Examiner cannot cite to art teaching sequestration or 100 hour dosing because these elements **did not exist** prior to Applicants invention. Prior to Applicants invention

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established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. . . . a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.. . . it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.").

[4] *See* also *MPEP* 2143.02 **entitled** "Reasonable Expectation of Success Is Required".

[5] *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 417 F. Supp. 2d 341, 371 (Fed. Cir.2006) ("While a reasonable expectation of success must be shown, in order to show *prima facie* obviousness it is not necessary to show that success was absolutely predictable."); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (discussing the obviousness case and stating that one element is "whether the prior art would also have revealed that . . . those of ordinary skill would have a reasonable expectation of success."). *See also*, MPEP 716.02(a) ("Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness.").

the dosing regime was much more frequent due to the rapid clearance of FIX from the blood, and sequestration of FIX did not exist.[6]

Even in the wake of *KSR Int'l Co. v. Teleflex Inc.* (127 S. Ct. 1727 (U.S. 2007)), Applicants know of no legal principle that suggests that a *prima facie* case can be maintained where two claimed elements are not found in the prior art. Thus, in the absence of these elements, the obviousness rejection cannot be maintained because the *prima facie* case is not made.

e) Several Missing Elements

In addition to the sequestration and dosage elements, the following elements are also not found in the cited art:

i) preventing hemophilic bleeding in advance of a bleeding event
ii) at least 90% monomeric after-aerosolization
iii) 80% activity retained after-aerosolization
iv) does not have ethanol
v) slowly maximally inhaling

All of these elements are merely assumed to exist in Lechuga, even though the formulation taught therein is not identical.

f) Kurachi Irrelevant

Kurachi is insufficient to show monomeric content of an aerosolized FIX. FIX structure *in vivo* is irrelevant because the *in vivo* environment is nothing like the claimed environment. The claims refer to **aerosolized** FIX and the art teaches that the process of aerosolizing FIX

[6] Examiner states that "Examiner does not understand Applicants arguments as to why the difference between intravenous administration of Factor IX is relevant to overcoming the *prima facie* obviousness case." The only treatment for hemophiliacs available today is needle based treatments. Thus, it is the **closest** prior art relating to the claimed treatment method and it clearly teaches away.

denatures it.[7] Applicants are not disputing that active FIX is a monomer *in vivo*, but its *in vivo* structure tells us nothing about what the dried, aerosolized FIX will look like and it is a well known fact that many proteins clump or otherwise deteriorate on such treatment.[8] The fact that Kurachi teaches that FIX is a monomer in the blood does not teach anything about the state of FIX in Lechuga, and Examiner's deduction regarding same is not logical.

g) Formulations Not Identical, Thus Recited Elements Still Missing

Examiner asserts that the observation of unknown properties of the Lechuga formulation are not novel. However, the formulations are **not** identical:

Lechuga	Closest Formulation Described in 10/820,656
37% FIX, 3% NaCitrate, 60% Leucine	32.6% FIX, 7.4 % NaCitrate, 60% Leucine
56% FIX, 4% NaCitrate, 40% Trileucine	52.6% FIX, 7.4 % NaCitrate, 40% Trileucine

One cannot **assume** that the Lechuga FIX has the requisite properties **because the formulations were not identical**. There is simply no way to get from Lechuga to an aerosolized FIX having the recited characteristics and providing sequestration and at least 100 hrs of dosing per the recited treatment claims without several assumptions and these assumptions cannot be properly made under established inherency principles (as shown below).

h) Inherency Used to Provide SEVEN Missing Elements

Inherency can be used to supply a missing element that is not expressly taught in the art, but which nonetheless **must** be present and would be so understood to be present in the prior art. *Astra Aktiebolag v. Andrx Pharms., Inc.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007) ("a prior art reference without express reference to a claim limitation may nonetheless anticipate by

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[7] Gupta, Pulmonary Delivery of Human Protein C and Factor IX Oxygen Transport to Tissue XVIII, Chapter 55, p. 429-435 (1997) ("in the process of being aerosolized human Factor IX is **50% denatured** at the air water interface.")(emphasis added).

[8] *See e.g.*, Choi et al., Inhalation delivery of proteins from ethanol suspensions, Applied Biological Sciences 98(20): 11103-11107 (2001) ("protein powders, at least as conventionally made, are liable to **clump** formation").

inherency."); *EMI Group N. Am., Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350 (Fed. Cir. 2001) ("A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim.") (cite omitted).

However, Applicants know of no case where inherency was used to provide at least seven of eleven claimed elements:

#	Claimed Invention Per Claim	Lechuga
1.	Preventing hemophilic bleeding in advance of a bleeding event	General treatment use suggested ("useful in the treatment of hemophilia B"), BUT "advance" or "prophylactic" treatment not taught
2.	Aerosolizing monomeric Factor IX (FIX)	See Table 15 (does not show monomer, see 90% monomer element below)
3.	MMAD of between 2 and 4 μm	See Table 15
4.	FPF % < than 3.3 μm of at least 50%	Lechuga teaches FPF generally, but not in relation to FIX and **NOT** the same as that claimed. "The powders of the invention . . . possess FPF values ranging from about 35%-85%. Such powders contain at least about 35 percent of aerosol particle sizes below 3."
5.	90% monomeric	Aerosolized monomers neither taught nor mentioned in Lechuga
6.	After-aerosolization activity is at least 80%	Post-aerosol activity neither taught nor mentioned in Lechuga
7.	Less than 10% water (wt/wt)	Water content of FIX neither taught nor mentioned in Lechuga, but Lechuga states generally that the moisture content of a dry powder is low ("'Dry powder' refers to a powder composition that typically contains less than about 20% moisture...most preferably contains less than about 3% moisture, depending upon the particular formulation."). Therefore, unknown FIX water content **may be higher** than that claimed. Lechuga also teaches the use of liquid formulations that are preferred ("The compositions described herein may be in powdered form or may be flowable liquids. **Liquid formulations are preferably solutions in which the active drug is dissolved in a solvent** (e. g., water, ethanol, ethanol-water, saline)").
8.	Does not have ethanol	Ethanol content of FIX not taught. Instead **teaches away** ("Liquid formulations are preferably solutions in which the active drug is dissolved in a solvent (e. g., water, **ethanol**, ethanol-water, saline)", also "The aqueous formulation may optionally contain additional water-miscible solvents, such as acetone, **alcohols** and the like."). However, Applicants have shown that this degrades FIX, and thus avoidance of ethanol is a claimed element.
9.	Slowly maximally inhaling aerosolized monomeric FIX	Slow maximal inhalation is not neither taught nor mentioned in Lechuga. Inhaled delivery of drugs in general is taught, but slow maximal inhaled delivery of aerosolized monomeric FIX to lungs is not taught.
10	Allowing said monomeric FIX to	Single statement regarding delivery to the "deep lung" is

	deposit in the deep lung tissue such that said monomeric FIX is sequestered in said deep lung tissue	present, but not in relation to FIX, nor is sequestration in the lung taught or mentioned in Lechuga.
11	To provide sufficient FIX to prevent bleeding for at least 100 hours after administration.	100 hour dosage neither taught nor mentioned in Lechuga. **Prior art teaches frequent use.** See BeneFix package insert.

Thus, Examiner assumes **seven of eleven** elements are present based on the inherent teachings of Lechuga. This seems to be stretching inherency principles to near invisibility.

i) Allegedly Inherent Elements Not "Necessarily Present"

Inherency cannot be based on what **might or might not** be present. *In re Oelrich,* 666 F.2d 578, 581-82 (C.C.P.A. 1981) ("To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference...Inherency, however, may not be established by probabilities or possibilities...") (emphasis added). Here, since the formulations are **not** identical, one cannot **assume** that the requisite properties were in fact present. There is simply no basis to assume that the formulation of Lechuga has all of the recited characteristics and would be sequestered in the lung sufficient to provides for at least 100 hours of dosing.

j) Assumptions Not Reasonable

Examiner asserts that the formulations of Lechuga are "substantially the same" and that "there is no indication from Applicants' data in the specification that it is critical for the compositions to...exhibit the claimed aerodynamic properties and physiological 'depot' effects."[9] This is not in accord with common sense. It should be readily apparent to anyone of ordinary skill in the art that it is critical for the FIX to be monomeric and to have sufficient activity (at least 80%) for any physiological effect to be seen. Similarly, the remaining characteristics are also known to be important for deep lung deposition and stability, that is why they are included in the basic claim.

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[9] Citrate is not claimed.

Even though the cited art shows that drying powders causes clumping[10] and that the only example of aerosolized liquid FIX was denatured, the Examiner insists on maintaining that he "reasonably expected that the prior art compositions upon administration by inhalation would exhibit the same depot effect." Until the Examiner declares under oath that such alleged facts are true, they are mere argument, and can be rebutted by prior art statements proving that the art is not as predictable as assumed by the Examiner.

k) Burden Improperly Shifted

Examiner is improperly shifting the burden to prove that two non-identical formulations are not the same. This is incorrect because to establish an inherent property, Examiner must **first** show that the property is **necessarily** present. *In re King*, 801 F.2d 1324 1327 (Fed. Cir. 1986) (**after** the PTO establishes a *prima facie* case of anticipation based on inherency, the burden shifts to appellant to 'prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.'")[11].

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[10] *See e.g.*, Choi et al., Inhalation delivery of proteins from ethanol suspensions, Applied Biological Sciences 98(20): 11103-11107 (2001) ("protein powders, at least as conventionally made, are liable to **clump** formation"); US6645466 ("Microfine particles, however, have a very unfavorable, i.e. large, ratio of surface to volume or mass and therefore a large surface energy. This is manifested in strong adhesion and cohesion tendencies which in turn lead to **poor flow properties** and to **powder aggregation**"); US20070235029 ("To facilitate pulmonary delivery, drug powders should normally be less than 5 μm ...However, powders of such small sizes...have very strong inter-particle forces that make them **agglomerate** and very difficult to handle. The agglomeration of powder is normally formed prior to delivery due to the inter-particle forces, and possible moisture absorption. Agglomerated drug powders become difficult to dispense completely from the doses, and/or, is dispensed at least partially as larger agglomerates, thereby significantly reducing the lung deposition efficiency."). *On inhaling drugs that heal, not harm*, The Hindu (2001) at http://www.hinduonnet.com/thehindu/2001/10/25/stories/08250003.htm ("There are, however, some issues that need to be addressed when delivering medication as solids and dry powders. They tend to **clump** and thus are hard to aerosolize or puff through. They require complex inhalers, and suffer from reproducibility problems. On the manufacturing side, they pose problems of preparation and packaging.").

[11] *See also, In re Simpson,* 102 Fed. Appx. 675, 678 (Fed. Cir. 2004) (non-precedential) ("the existence of the **same** structural elements in Rilitz gave both the examiner and the Board a reason to believe that these elements could perform the same functions claimed by Simpson. The

l) Competant Evidence Requested

If the Examiner is unwilling to provide a Declaration under penalty of law that the Lechuga formulation possesses **all** properties identical to those claimed, then Examiner's speculation as to the similarity of the formulations is mere argument, not fact. *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993) (holding that "the Board did not err in determining that Fiers presented no convincing evidence" where applicant only showed "argument ... 'unsupported by competent evidence, entitled to little or no weight and ... unpersuasive in any event.'"); *In re Juillard*, 476 F.2d 1380 (C.C.P.A.) ("arguments cannot take the place of evidence"). Applicants expressly challenge these assumptions as not properly Officially Noticed and request that Examiner support all findings with adequate evidence pursuant to MPEP 2144.03.[12]

m) Obviousness Case not Properly Based on Unknown Inherency

Even if the formulations were identical, it is not proper to make an obviousness case based on **unknown** inherent properties of the Lechuga formulation. *In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("That which may be inherent is not necessarily known. **Obviousness cannot be predicated on what is unknown.**") (citations omitted).

It was not known under Lechuga that any formulation of FIX could be sequestered and thus produce at least 100 hrs of dosing. It could not be predicted from Lechuga because Lechuga never used an aerosol to treat an animal or patient, much less to produce the sequestration effect allowing for less frequent dosing.

The dog study performed by inventors and shown in Example 1 of the specification shows proof of concept—that FIX can be absorbed when a liquid FIX is deposited on the back of

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burden therefore shifted to Simpson to disprove inherency."). Here, the formulations are not the same, and the burden cannot be prematurely shifted.

[12] MPEP 2144.03 (Stating that "It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. . . It is never appropriate to rely solely on 'common knowledge' in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based.")

the throat. However, it does not show FIX deposition in the deep lung, nor sequestration, nor 100 hour dosing. Assuming both sequestration and 100 hour dosing is a clear application of hindsight reasoning. *KSR Int'l Co.* at 1742 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.").

n) Prior Art Treatments Teach Away

Examiner states that "Examiner does not understand Applicants arguments as to why the difference between intravenous administration of Factor IX is relevant to overcoming the *prima facie* obviousness case."

The **only** treatment for hemophiliacs available today is IV and other needle based treatments. Thus, this is the **closest** prior art relating to the claimed treatment method and it clearly teaches **away** from both sequestration and 100 hour dosing.[13]

o) Gupta Teaches Away

Examiner states that "the problems associated with the nebulization of aqueous solutions of proteins (e.g. Factor IX) are irrelevant with regards to the suggested method of Lechuga." However, Gupta[14] is the **only** prior art effort to aerosolize FIX and determine its subsequent activity. Even though Gupta teaches activity loss in liquid FIX, the formulation made by the inventors is also liquid prior to being dried, and the potential for loss of activity is similarly present. Gupta is relevant because it is the **closest** prior art related to the recited activity element (at least 80%). Yet Gupta teaches that the FIX was denatured when aerosolized. Many protein

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[13] *See, e.g.*, BeneFix package inserts at http://www.wyeth.com/content/ShowLabeling.asp?id=92 or http://www.fda.gov/cber/label/cfixwye071106lb.pdf showing 18.8 ± 5.4 or 20.2 ± 4.0 hour half lives and recommending 12-24 hour dosing. See also Fig. 8 in the specification showing head-to-head comparison of pharmacokinetics of IV versus inhaled FIX.

[14] Lechuga (WO0132144) fails to demonstrate the activity or form of spray dried FIX—thus, Lechuga also fails to establish a reasonable expectation of success.

treatments are known to cause activity loss,[15] and based on this and the teachings of Gupta, it is not reasonable to **assume** protein activity in the absence of proof of same.

p) Unexpected Results Found in Sequestration

Even if the *prima facie* case were made, Applicants have provided competent evidence of unexpected results in the sequestration effect (see Application, Fig. 8 showing IV profile with very high initial dose and rapid loss, as well as inhaled profile with dose remaining constant for at least 100 hrs). *See also* BeneFix package insert[16] confirming the rapid clearance of FIX in the prior art.

The pharmacodynamic profile of inhaled FIX is a significant (and surprising) improvement over the intravenous FIX profile because it **avoids the large initial dose** and thus clotting difficulties due to the initial high dose of FIX (see e.g., BeneFix package insert[17] noting that "use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications")[18], and because the **dose remains constant** for at least 100 hours. Further, based on the surprisingly flat profile shown in Figure 8, one would expect that the FIX would remain sufficiently high to prevent excess bleeding for at least one week. Thus, the clinical importance of this unexpected effect is also shown. This unexpected (and claimed) effect is sufficient to rebut a *prima facie* case of obviousness.

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[15] *See e.g.*, Choi et al., Inhalation delivery of proteins from ethanol suspensions, Applied Biological Sciences 98(20): 11103-11107 (2001) ("protein powders, at least as conventionally made, are liable to **clump** formation").

[16] See e.g., http://www.wyeth.com/content/ShowLabeling.asp?id=92 or http://www.fda.gov/cber/label/cfixwye071106lb.pdf (two slightly different BeneFix package inserts providing half lives of 18.8 ± 5.4 hours or 20.2 ±4.0 hours).

[17] E.g., http://www.wyeth.com/content/ShowLabeling.asp?id=92

[18] *See also*, Astrid van Hylckama Vlieg, *et al.,* **High levels of factor IX increase the risk of venous thrombosis,** Blood, 95(12):3678-3682 (2000) (emphasis added).

q) Examiner Summarily Dismisses Head-to-Head Data

Examiner summarily dismisses the evidence of unexpected results as "off point" since its relates to IV and not inhalation treatments. However, the BeneFix package inserts showing an 18-20 hr half life is the **closest prior art** relating to the treatment element, and Examiner has not cited **any** other prior art showing treatment.[19] It is procedurally incorrect to summarily dismiss all prior art that unfortunately teaches away from the invention as "off point."

Further, the pharmacokinetic data is reproduced by inventors in a head-to-head measurement of IV versus inhalation pharmacokinetics—data even the FDA would accept in making a direct drug comparison claim. There is no rationale basis for ignoring this data, and its summary dismissal is both arbitrary and capricious.

r) Prior Art and In Vivo Data Provide Competent Evidence

Applicants have shown **published statements** by Gupta and others in the field evidencing no reasonable expectation of success and ***in vivo* head-to-head comparative data** showing unexpected effects, thus rebutting the *prima facie* case. Competent rebuttal evidence taken as a whole should be weighed against the evidence supporting the *prima facie* case. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). See also MPEP 716.01(d). In this case, there is **no** competent evidence for the opposing case. Thus, as a matter of law the unsupported rejections should be withdrawn.

CONCLUSION

The Examiner has failed to provide any support for two of the recited claim elements, and has assumed the existence of another five elements based on an prior art formulation that is not even identical to that taught in the cited art. Thus, seven elements are missing from the cited art and the *prima facie* case is not made.

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[19] Lechuga does not show inhalation treatment with FIX, but only states what was already known in the art—that FIX could be used to treat hemophilia.

Further, Applicants have provided evidence of non-obviousness (teaching away in the prior art and *in vivo* data showing an unexpected result) sufficient to rebut a *prima facie* case. Thus, as a matter of law the claims cannot be held to be obvious and Applicants request their allowance.

If any questions or issues remain in the resolution of which the Examiner feels will be advanced by a conference with the Applicants' attorney, the Examiner is invited to contact the attorney at the number noted below. The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 50-3420 (reference 31176282-004001 Valoir).

Dated: December 21, 2007

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